Gastric Ulcers Following Vagotomy in Swine

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WHEN division of the vagus nerve to the stomach for the treatment of peptic ulcer was first done by Dragstedt and associates [4] the operation was performed by a transthoracic approach. The vagus nerves were divided but an additional drainage procedure such as gastroenterostomy or pyloroplasty was not added. Approximately 150 patients were operated upon in this way and the majority secured a good result and remained well. Many, however, developed unpleasant symptoms due to stasis of food in the stomach, gastric distension, belching and episodes of diarrhea. Seven of these patients were found to have developed gastric ulcers from 2 to 5 years after the vagotomy. The fasting, nocturnal or basal secretion in these patients was found to be less than normal and several displayed no free acid in the basal secretion. The development of gastric ulcers in patients whose gastric secretion had been profoundly reduced by division of the vagus nerves to the stomach seemed at first to question the view that these lesions were of peptic origin. However, the observations of Palmer and associates [10] that gastric ulcers usually healed when anacidity was produced by x-ray therapy to the stomach and that these ulcers recurred when the gastric glands regained the ability to secrete acid and the common observation that gastric ulcers usually heal following the same type of alkalinazation therapy found effective in duodenal ulcers suggested that some other explanation was required.

Before the development of gastric ulcer as a complication of vagotomy for duodenal ulcer was observed, a drainage procedure such as gastroenterostomy and pyloroplasty was added to vagotomy to prevent gastric stasis and its accompanying disabilities. The disappearance of gastric ulcer as a complication of vagotomy when these drainage procedures were employed, suggested that stasis of food in the stomach might be the cause of these lesions. It had been observed that patients with stenosing duodenal ulcers, treated by medical measures, occasionally develop a secondary gastric ulcer as a complication.[6] This clinical observation was substantiated in our laboratory by the finding that experimental pyloric stenosis in dogs with Heidenhain pouches caused gastric stasis and a prolonged hypersecretion of gastric juice.[12] Several of these animals developed chronic progressive gastric ulcers closely resembling the chronic lesion.[2] In the present experiments chronic gastric ulcers have been produced in rats by a similar type of pyloric stenosis produced by cellophane bands (Fig. 1).

It is probable however that most patients with gastric ulcers do not have an accompanying duodenal ulcer or organic stenosis

Submitted for publication January 9, 1969.

This work has been aided by Grants AM-04178 and AM-02372, from the Division of Research Grants and Fellowships of the National Institutes of Health, U. S. Public Health Service.

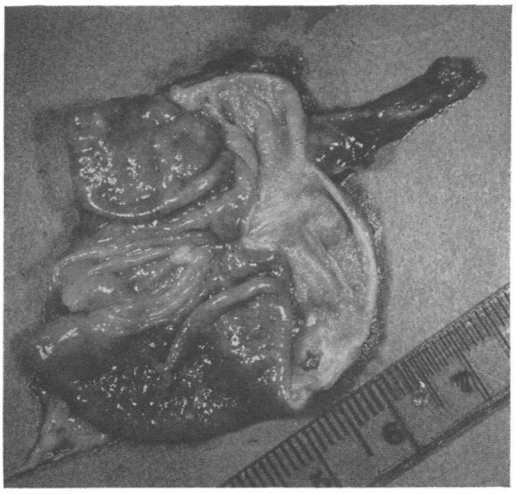

FIG. 1. Photograph of a chronic gastric ulcer which was found in a rat 322 days after pyloric stenosis had been produced by a cellophane band.

at the pylorus. Furthermore, these patients have been found to put out less free hydrochloric acid in the basal secretion than do normal people. These findings have led some observers to state that a hypersecretion of gastric juice does not exist in gastric ulcer patients. It should be recalled, however, that the basal secretion is largely of nervous origin and that activation of the hormonal mechanism is usually produced by the presence of food in the stomach. As a consequence the amount of hormonal secretion in patients is difficult to determine and relatively few observations of its extent in health and disease have been made. In experimental animals however, provided with Heidenhain pouches, the significance of the hormonal mechanism is easily demonstrated. It has been found that stasis of food in the main stomach produced by vagotomy causes a long continued hypersecretion of gastric juice from the Heidehain pouch.[5, 13] The addition of a drainage procedure such as gastroenterostomy prevents this hypersecretion.

Recent studies on the physiology of gastric secretion indicate that vagotomy reduces the secretion of gastric juice by at least 3 effects: (1) The psychic or nervous phase of gastric secretion is abolished, (2) The sensitivity or responsiveness of the gastric glands is profoundly reduced, and (3) The vagal release of gastrin is abolished. In view of these facts it does seem strange that a hypersecretion of gastric juice of hormonal origin can occur after total gastric vagotomy. However, in recent experiments [3] it has been observed in this laboratory, that stasis of food in the stomach, produced by vagotomy in dogs with Heidenhain pouches can cause a profound hypersecretion even if the antrum mechanism has been further handicapped by the operation of antroneurolysis. In this procedure the connections between the antrum mucosa and underlying structures were severed by a surgical operation.

Many years ago Van Yzeran [14] reported that rabbits developed chronic gastric ulcer after division of the vagus nerves to the stomach. This observation was confirmed by Beazell and Ivy.[1] In 1964 Linares and associates [7] in this laboratory found that these chronic gastric ulcers produced by vagotomy in rabbits could be prevented by the addition of gastroenterostomy or pyloroplasty to the operation thus supporting the impression obtained from the clinical experience in man. Although repeated attempts have been made to produce chronic gastric ulcers by vagotomy in dogs in this laboratory, the results have been negative. Even vagotomy combined with extensive intestinal resection failed to produce any gastric ulcers. Although vagotomy in rats has been reported to produce chronic gastric ulcers in this species in the present experiments the results were entirely negative. Spontaneous gastric ulcers in dogs and rats however are exceedingly rare and it may well be that these species have a high resistance to such lesions.

Recent studies however, have made it quite evident that spontaneous ulcers in the stomach of swine are not unusual and

FIG. 2. Photograph showing a small gastric ulcer and a punctate erosion found in swine 114 twenty-two days after vagotomy.

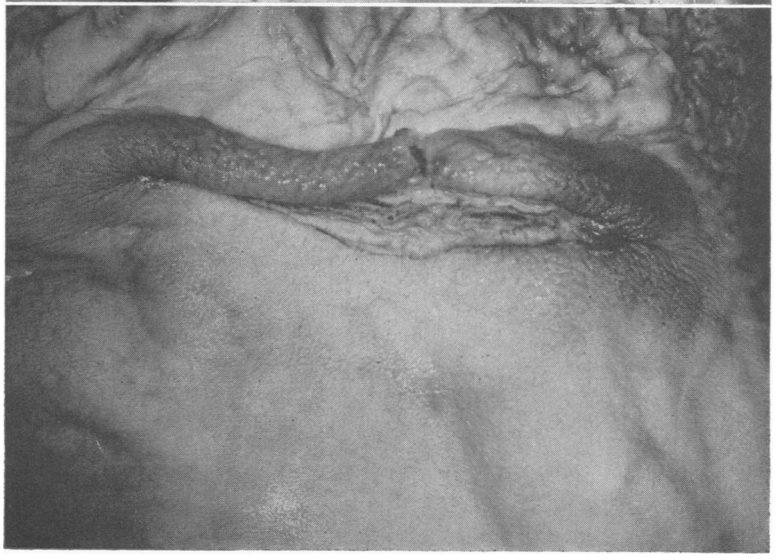

FIG. 3. Photograph showing a large, linear ulcer in the glandular portion of the stomach adjacent to the squamous epithelium of the esophagus in swine 123 thirty-two days after vagotomy.

many papers have appeared in the veterinary literature concerning this disease. Nutritional and environmental factors have been examined and ulcers have been produced in swine by the repeated injection of both histamine [9] and reserpine.[8]

This evidence that swine are apparently more vulnerable to the development of chronic gastric ulcers than are most other species suggested that this might be the appropriate animal to study the effect of vagotomy in the production of chronic gastric ulcers.

Experimental Procedure

A. Acute Effects of Vagotomy in Swine. Thirteen swine of Duroc stock were secured as weanlings, vaccinated against hog cholera, and the males were castrated. They were housed in indoor-outdoor concrete pens with a constant supply of fresh water and protection from the sun. They

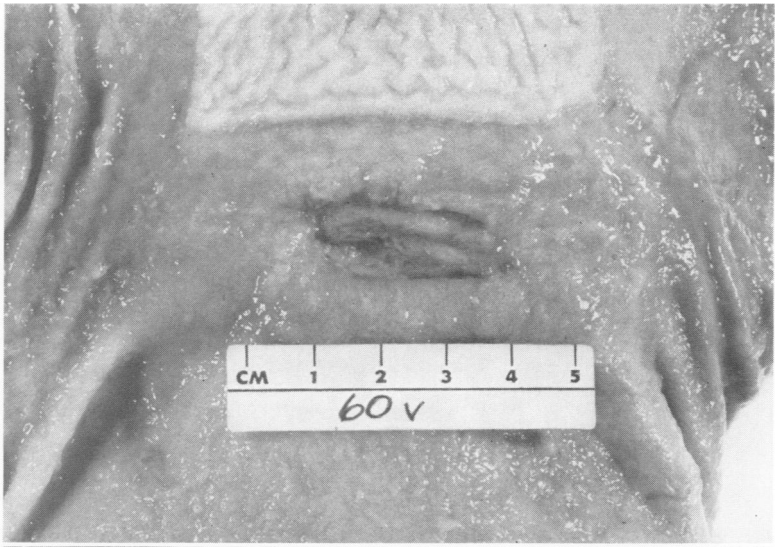

FIG. 4. Photograph showing a large chronic ulcer in the stomach of swine 60 sacrificed 137 days after vagotomy.

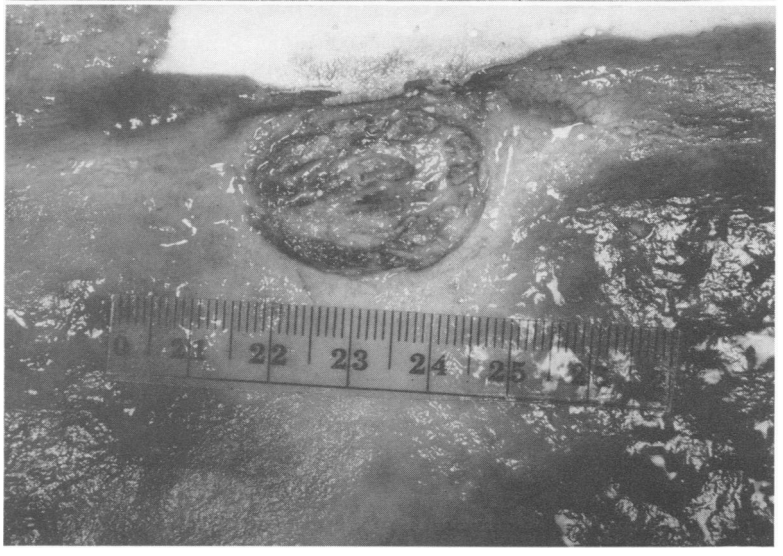

FIG. 5. Photograph showing a large chronic ulcer in the stomach of swine 121 found dead 141 days after vagotomy.

were fed the standard swine ration prepared by the University of Florida Animal Husbandry Department. At the time of surgical operation they weighed between 28 and 46 pounds.

The swine were anesthetized with ether, methoxyflurane, or pentobarbital, a midline incision made, and the upper portion of the stomach and the lower esophagus were exposed. Both vagus nerves were readily found, divided, and a short segment of nerve excised between silk ligatures. Three of the swine served as controls. These were operated upon in the same way except that the vague nerves were not divided. Recovery was prompt and uneventful and for the first week the animals were given water ad libitum and a small amount of the swine ration mixed with water daily. Thereafter they were fed the usual swine ration ad libitum. The vagotomized swine ate the food quite as readily as the controls and made a comparable gain in weight.

They were sacrificed from 2 to 8 weeks following operation. Each animal received water but no food for 48 to 96 hours before death so stasis of food in the vagotomized stomach could be determined. A small ulcer (3 x 3 mm.) and a punctate erosion were found in swine 114 twenty-two days following vagotomy (Fig. 3). Similar erosions were found in three other swine sacrificed after 2 to 4 weeks. No gross lesions were found in the remaining seven vagotomized swine, nor in the controls, sacrificed 5 to 8 weeks after surgery. The stomachs of the vagotomized swine all contained food, the amount varying from 3 Kg. to 4 Kg. in weight. In most of the animals the distention of the stomach was remarkable, especially in view of the 48-hour fast. In sharp contrast the stomachs of the control swine contained from 30 to 90 cc. of a thick, yellow, tenacious fluid but no food. The pH of the gastric content of the vagotomized swine varied between 2.8 and 4.5 and that of the controls between 4.7 and 5.55. The pH of the swine ration mixed with water was 6.05.

B. Chronic Effects of Vagotomy in Swine. Nine swine of Hampshire and Poland China stock were secured as weanlings, vaccinated against hog cholera, and the males castrated. The vagus nerves to the stomach were divided in seven swine, as described in A, while 2 were kept as controls. They were housed and fed in the same way.

Swine 123 died 32 days after vagotomy from volvulus of the small intestines and peritonitis. A large, linear ulcer was found on the posterior wall of the glandular portion of the stomach adjacent to the squamous epithelium of the esophagus (Fig. 3).

Swine 60 was sacrificed 137 days after vagotomy. The stomach was distended and contained 6½ Kg. of food, acid in reaction. An ulcer (2 x 2 cm.) was found on the posterior wall of the glandular mucosa of the stomach 1 cm. from the squamous epithelium of the esophagus (Fig. 4).

Swine 121 died 141 days after vagotomy from unknown causes. An ulcer (3 x 2 cm.) was found on the posterior wall in the glandular mucosa of the stomach extending to the squamous epithelium of the esophagus (Fig. 5).

Swine 89 was sacrificed 143 days after vagotomy. The stomach was markedly distended and contained 7 Kg. of food although no food had been given during the previous 48 hours. An ulcer (2 x 2 cm.) was found on the posterior wall of the glandular portion of the stomach about 1 cm. from the squamous epithelium of the esophagus (Fig. 6).

Swine 174 was sacrificed 157 days after vagotomy. The stomach was distended and contained 6 Kg. of food although no food had been given during the previous 48 hours. An irregular shallow ulcer (2½ x 3 cm.) was found on the posterior wall of the glandular portion of the stomach about 5 cm. from the squamous epithelium of the esophagus (Fig. 7).

Swine 83 (Fig. 9) was sacrificed 265 days after vagotomy. The stomach contained 4.1 Kg. of food although no food had been given for the previous 48 hours. A sharply punched out deep ulcer (2 x 2 cm.) was found on the posterior wall of the stomach (Fig. 8).

Swine 175 (Fig. 9) was sacrificed 275 days after vagotomy and the control swine 88 and 64 were sacrificed 141 and 253 days, respectively, after the dummy operation. No lesions were found in the stomachs of these animals.

Discussion

Although chronic gastric ulcers have been reported as occurring not infrequently in swine, no such spontaneous lesions were encountered in this investigation. The five swine designated as controls had no abnormalities in the gastric mucosa when

FIG. 6. Photograph showing a large chronic ulcer in the stomach of swine 89 sacrificed 143 days after vagotomy.

FIG. 7. Photograph showing a shallow irregular ulcer in the stomach of swine 174 sacrificed 157 days after vagotomy.

sacrificed. In the acute experiment where the swine were sacrificed within a period of 8 weeks no gastric lesions were found in seven although vagotomy had been done. Thus in the entire experiment 12 swine had normal stomachs. In contrast, of the seven swine in the chronic experiment six or 85 per cent developed chronic gastric ulcers from 32 to 265 days after bilateral gastric truncal vagotomy. The spontaneous ulcers reported in swine have almost always been found in the squamous epithelium which in swine extends for a variable distance from the esophagus into the stomach. The lesions have been characterized as esophago-gastric ulcers. No such ulcers were found in our swine. The lesions which developed after vagotomy in swine were remarkably uniform in location. All occurred on the posterior wall of the stomach near the lesser curvature and adjoining or within two or three centimeters of the squamous epithelium of the esophagus. It recalls the observations of

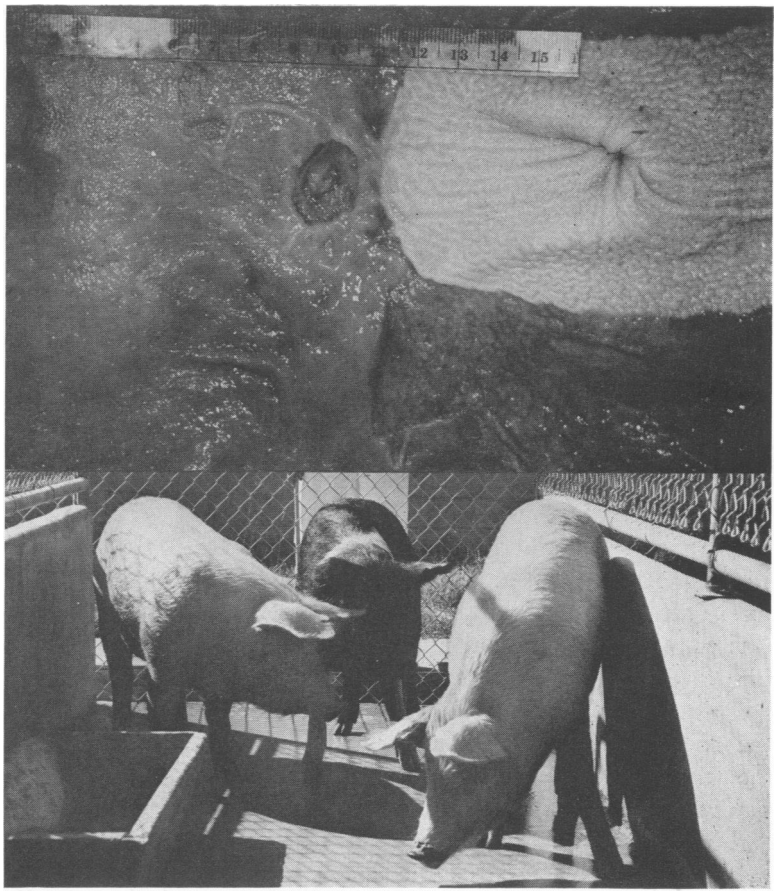

FIG. 8. Photograph showing a sharply punched out chronic ulcer in the stomach of swine 83 sacrificed 265 days after vagotomy.

FIG. 9. Photograph showing the growth of vagotomized swine and a control. Swine 83 on the left and swine 175 on the right were vagotomized while the center animal from the same litter had only a dummy operation. All three gained weight at the same rate.

Minoru Oi of Tokyo that the majority of the gastric ulcers in his long series occurred near the junction of the acid secreting corpus and the antrum mucosa. Is this an area of less resistance? All of our ulcers developed in the glandular portion of the stomach and although near, none appeared in the squamous epithelium of the esophagogastric area. This fact suggests that the spontaneous ulcers in swine may not be peptic in origin.

Abnormal stasis of food in the stomach was found in all of the vagotomized swine. The stomachs were uniformly distended with partially digested food 48 and even 96 hours after the last meal. The pH of the gastric content varied between 2.8 and 4.5. In contrast the stomachs of the control swine were empty of food and the mucoid fluid in the stomach varied between pH 4.7 and pH 5.55. These findings are in harmony with the experimental observations on dogs [5, 12, 13] and rabbits [7] with Heidenhain pouches. In these animals stasis of food either as a result of pyloric stenosis or vagotomy produced a profound increase in the pouch secretion. While the mechanical effect of distention and prolonged contact with food cannot be entirely discounted it appears probable that the chronic gastric ulcers which developed in swine from 32 to 265 days after bilateral vagotomy in these experiments were peptic in origin. The prolonged contact of food with the antrum mucosa has caused a prolonged release of gastrin with continued stimulation of gastric secretion until the stagnant gastric contents have become

sufficiently corrosive to break down the gastric mucosa and produce and maintain the lesions.

In spite of the gastric atony and prolonged emptying time of the stomach the vagotomized swine grew just as rapidly as the controls and when sacrificed weighed just as much (Fig. 9). These observations support the employment of vagotomy and a drainage procedure in preference to partial gastrectomy in the surgical treatment of duodenal ulcers in children.

Summary

Large chronic gastric ulcers developed in 6 of 7 swine from 32 to 265 days after division of the vagus nerves to the stomach. Of 10 swine examined from 2 to 8 weeks after vagotomy, a small gastric ulcer was found in one animal and gastric erosion in 3 others. The remainder displayed no gastric lesions and none were found in the control litter mates. The stomachs of the vagotomized swine were markedly distended with partially digested food 48 to 96 hours after the last meal. It is suggested that the cause of these gastric ulcers is a hypersecretion of gastric juice of humoral or gastrin origin due to long continued contact of food with the antrum mucosa. As a result of this continued secretion of gastric juice the stagnant gastric contents became sufficiently corrosive to break down the mucosa, produce and maintain the gastric ulcers.

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